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Thank you.

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Blood pressure and left ventricular anatomy and function after heart transplantation

To determine whether hypertension occurring after heart transplant causes the development of cardiac hypertrophy, changes in pressure load (N = 13) and left ventricular anatomy (N = 11) were evaluated up to 1 year after heart transplant in a prospective longitudinal study. Pressure load was evaluated by 24-hour ambulatory blood pressure monitoring, and left ventricular anatomy and function were assessed by M-mode echocardiography under two-dimensional guidance. Body weight increased by 11 to 12 kg. Blood pressure showed a gradual increase during the first few months after transplant: diastolic pressure by 15 to 18 mm Hg and systolic pressure by 12 to 15 mm Hg, with hypertension persisting during the night. Nearly all patients required treatment with one or two antihypertensive drugs. The increase in blood pressure was related to increased total peripheral resistance with minor decreases in cardiac output. Both septal and posterior wall thickness and left ventricular mass (by 25 to 30 gm/m^2) decreased during the initial months after transplant and subsequently remained at "normal" levels (100 gm/m^2). The persistence of normal left ventricular mass may indicate either that the increases in daily pressure load and body weight were not sufficient to induce myocardial growth or that the latter was prevented by, for example, absence of cardiac sympathetic nerve activity. (Am Heart J 1991;122:1087.)

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Long-term increases in wall stress in the adult heart lead to increased protein synthesis, cellular growth, and hypertrophy. There is extensive evidence indicating that in hypertension development or regression of cardiac hypertrophy does not necessarily parallel the change in afterload, and other mechanisms can play an important modulating role. For example, arterial vasodilators such as minoxidil may actually increase the cardiac mass of rats with hypertension despite large decreases in blood pressure.[1] Besides cardiac volume overload,[2] a persistent increase in cardiac sympathetic activity[1, 3, 4] may explain these divergent changes. Regarding development of cardiac hypertrophy, studies in rats and cats have demonstrated that in these species cardiac sympathetic nerve activity is not essential for the development of cardiac hypertrophy in response to increased afterload.[5] In humans hypertension after cardiac transplantation provides a unique model to assess whether

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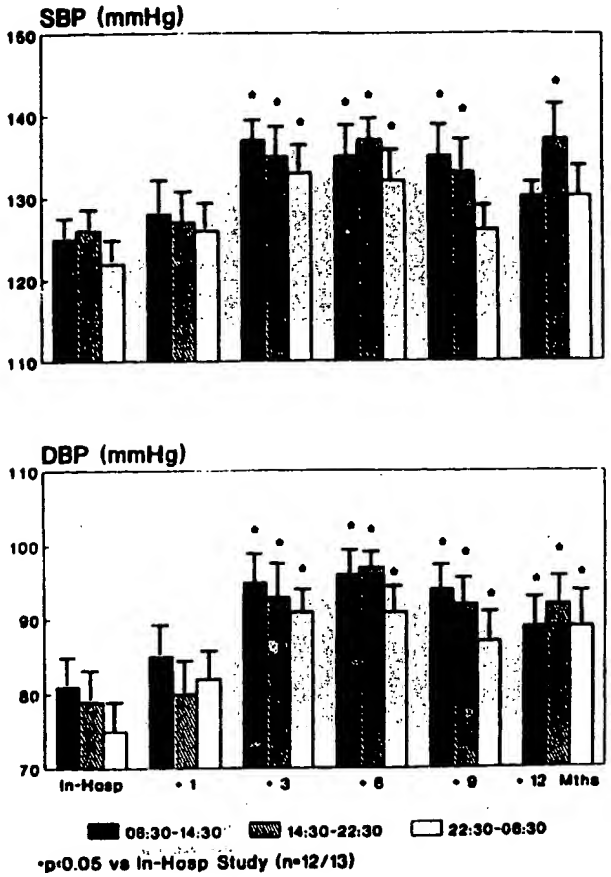

Fig. 1. Systolic and diastolic blood pressure after heart transplant as assessed by 24-hour ambulatory blood pressure monitoring. Values represent means ± SEM (n = 13 for up to 6 months and n = 12 for 9 and 12 months). $^*p < 0.05$ for change from in-hospital study.

cardiac sympathetic nerve activity plays a role in the development of cardiac hypertrophy in humans with hypertension. Hypertension develops within several weeks/months after transplantation in patients treated with cyclosporine.[6] One cross-sectional retrospective study[7] reported an increased left ventricular (LV) mass in cyclosporine-treated patients versus a control group early after surgery but not later (>12 weeks after transplant), whereas another cross-sectional study[8] reported a 17% increase 1.2 ± 0.8 years after surgery. In the present prospective longitudinal study, changes in pressure load and LV anatomy were evaluated up to 1 year after heart transplant. Despite increases in body weight and blood pressure, LV mass initially decreased and then remained at "normal" levels.

METHODS

Subjects. Eighteen subjects consented to participate in the study. Six of these patients (one because f severe rejection and five because of too great a traveling distance) did not continue f r the 1 year of follow-up. Data from 13 patients with at least 6 months of follow-up are included in the present data base. These 13 patients included 11 men and two women; the age at transplantation was 48 ± 3 years (mean ± SEM, range 21 to 59 years). Congestive heart failure was caused by coronary artery disease in seven patients and by idiopathic cardiomyopathy in six. For immunosuppression, patients received cyclosporine (150 to 800 mg/day), azathioprine (25 to 175 mg/day), and prednisone (12.5 to 35 mg/day). All patients were stable at entry into the study and on biopsy had no histologic evidence of significant rejection at the time of study, except for one instance of mild and one of moderate rejection at the 1-month studies. Among the 13 donors were 10 men and three women; the age at cardiectomy was 25 ± 3 years (range 14 to 43 years). Two of them had a previous history of mild hypertension.

Study protocol. Patients were first studied before leaving the hospital (23 ± 3 days [range 10 to 35 days] after surgery), except for two patients who were first studied shortly after they had left the hospital. Subsequent studies were performed at 1, 3, 6, 9, and 12 months after patients left the hospital. Antihypertensive drug therapy being taken by a patient was noted but was not discontinued for the study. For each study patients came to the hypertension unit in the morning to start 24-hour ambulatory blood pressure monitoring and 24-hour urine collection. After patients returned the next morning, body weight was obtained, a blood pressure cuff was applied, and an indwelling catheter was inserted into a forearm vein for blood sampling. Subsequently patients rested in a semisupine position in a semidark, quiet room, and an echocardiogram was obtained and blood pressure measured between 20 and 30 minutes of rest. At 30 minutes blood samples were taken for determination of plasma catecholamine levels, plasma renin activity (PRA), and serum electrolyte and creatinine levels. Subsequently the patient would stand quietly for 15 minutes, and blood samples for determination of plasma catecholamine levels and PRA were obtained at 5 and 15 minutes of standing.

Echocardiography. Technically satisfactory left ventricular echocardiograms were obtained from 11 patients. Echocardiograms were obtained with subjects in the supine position, turned 30 degrees on their left side, by means of a Toshiba Sonolayer SSH-60 A echo machine with a 3.75 MHz transducer in conjunction with a Toshiba Line Scan Recorder LSR-20B (Toshiba, Osaka, Japan). M-mode echocardiography was performed under two-dimensional guidance, and tracings were recorded at a paper speed of 50 mm/sec. Measurements were made to the nearest millimeter for at least four cardiac cycles during quiet respiration, and the means w re used for analysis.

All echocardiograms in a patient were obtained by the same research assistant with the patient in the sam position, in the same interc stal area, and in the same LV area, just below the tip of the mitral leaflets. Measurements were made by the same observer and were obtained acc rding to the guidelines of the American Society f Echocardiog-

Table I. Antihypertensive drug therapy during the first year after heart transplant

Drug	*In hospital*	*+1 mo*	*+3 mo*	*+6 mo*	*+9 mo*	*+12 mo*
β-Blockers	0	1	1	1	3	3
Angiotensin-converting enzyme inhibitors	2	1	2	2	2	3
Diuretics	4	3	3	3	3	3
Ca^{++} antagonists	2	3	6	8	8	7
Clonidine	0	0	0	3	2	2
Total	8	8	12	17	18	18
Patients receiving therapy	5/13	5/13	5/13	9/13	11/12	11/12

Table II. LV volumes, heart rate, and LV wall thickness after heart transplant

In hospital	*+1 mo*	*+3 mo*	*+6 mo*	*+9 mo*	*+12 mo*
LV end-diastolic volume (ml)					
120 ± 7	121 ± 11	113 ± 10	116 ± 10	111 ± 9	113 ± 10
LV end-systolic volume (ml)					
28 ± 4	33 ± 5	32 ± 5	33 ± 4	30 ± 4	33 ± 4
Fractional shortening (%)					
40 ± 2	37 ± 2	36 ± 2*	35 ± 2*	36 ± 2*	35 ± 1*
Heart rate (beats/min)					
84 ± 5	86 ± 4	88 ± 4	89 ± 3	86 ± 3	85 ± 4
Septal wall thickness, diastole (mm)					
10.7 ± 0.4	10.4 ± 0.4	10.0 ± 0.4	9.9 ± 0.4*	9.4 ± 0.3*	9.9 ± 0.4*
LV posterior wall thickness, diastole (mm)					
10.6 ± 0.3	10.2 ± 0.2	9.8 ± 0.3*	9.9 ± 0.3*	9.9 ± 0.2*	9.9 ± 0.3*

Values represent means ± SEM (n = 11 to 13).
*$p < 0.05$ for change from in-hospital study.

raphy.[9] The following parameters were measured or calculated: LV end-diastolic and end-systolic dimension, septal and posterior wall thickness in systole and diastole, and percentage of fractional shortening. LV mass was calculated according to the Penn formula[10]: 1.04x ([LV end-diastolic dimension + (septal + posterior wall thickness in diastole)]^3 − LV end-diastolic dimension^3) −13.6 and presented as both absolute values and mass index (gm/m^2). Considering the changes in water content (see Discussion), strictly speaking this should be presented as myocardial volume rather than myocardial mass. LV end-diastolic and end-systolic volumes, estimated by the cube-function formula from corresponding dimensions, were used to calculate stroke volume and cardiac index. Total peripheral resistance (TPR) was calculated from mean blood pressure (diastolic blood pressure + one-third pulse pressure) and cardiac index. LV end-systolic wall stress (ESS) was calculated as described previously.[11] Echocardiographic measurements were performed in a blinded fashion, and individual parameters were calculated with a DBase III program (Ashton-Tate, Culver City, Calif.).

Ambulatory blood pressure monitoring. A SpaceLabs 5200 device (SpaceLabs Inc., Redmond, Wash.) was applied between 9 and 11 AM to the nondominant arm. Accuracy was checked by means of a T tube and a mercury manometer for agreement of the mean of two readings within 10 mm Hg systolic and 5 mm Hg diastolic pressure. Pressure was recorded every 20 minutes throughout the day and every 60 minutes at night. The records were scanned for obvious artifactual data points (e.g., pulse pressure <20 mm Hg) but were otherwise not edited. A 24-hour period was divided into three periods (6:30 AM to 2:30 PM, 2:30 PM to 10:30 PM and 10:30 PM to 6:30 AM), and the averages of all systolic and diastolic blood pressure values per period were determined.

Analytical methods. Blood samples were centrifuged at 4° C. Plasma catecholamine levels were determined by radioenzymatic assay[12] and PRA by radioimmunoassay.[13] Urinary and serum sodium, potassium, and creatinine concentrations were measured by standard hospital procedures (flame photometry and autoanalyzer).

Statistical analysis. Results are expressed as mean ± SEM. Statistical analysis for changes from the "in-hospital" study was performed by analysis of variance for repeated measures with the SAS program (Statistical Analysis Systems, SAS Institute, Cary, N. C.). A p value of 0.05 or less was considered significant and was used in the figures; actual p values appear in the text.

RESULTS

Blood pressure

Ambulatory blood pressure (Fig. 1). Before patients left the hospital, blood pressure was still within the normotensive range for all three periods of the

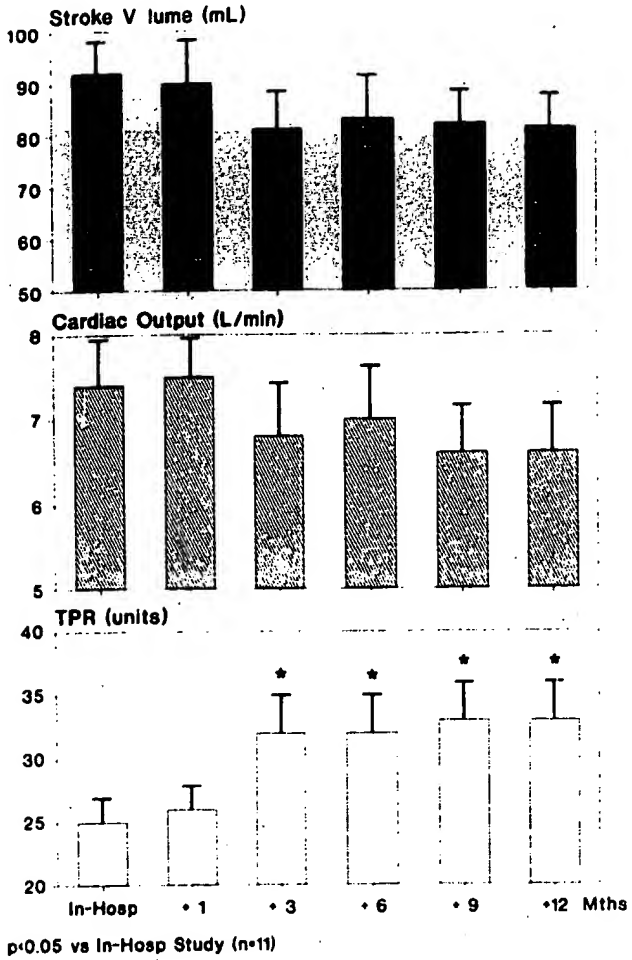

Fig. 2. Stroke volume, cardiac output, and total peripheral resistance *(TPR)* after heart transplant. Values represent means ± SEM (n = 11). *$p < 0.05$ for change from in-hospital study.

day. One month later blood pressure had increased somewhat (not significant [NS]) but was still in the normal range. At 3 months blood pressure had increased more markedly and remained at this level for up to 1 year of follow-up. Both systolic and diastolic blood pressure increased: diastolic pressure by 15 to 18 mm Hg and systolic pressure by 12 to 15 mm Hg. The three periods of the day showed a similar pattern of change, and nighttime blood pressure was only slightly lower than the daytime value.

Antihypertensive drug therapy (Table I). The previously described increases in blood pressure in the initial months after heart transplant and subsequent maintenance of the hypertension occurred despite increasing numbers of patients taking increasing amounts of antihypertensive drugs.

Left v ntricular function

LV volumes, cardiac output, and TPR (Table II and Fig. 2). LV volumes and cardiac output at the end of the hospital stay were in the normal range. Subsequently LV end-diastolic and end-systolic volume showed minor (NS) changes (Table II). Fractional shortening ($p < 0.05$), stroke volume ($p < 0.10$), cardiac output (NS), and cardiac index ($p < 0.05$ at 9 and 12 months, Fig. 2) decreased somewhat more. Heart rate was stable over the duration of the study (Table II). Inasmuch as blood pressure increased and cardiac index decreased, the calculated TPR increased by approximately 30% ($p < 0.01$, significant as of 3 months; Fig. 2).

Determinants of LV mass

Body weight (Fig. 3). During the first 6 months after transplant, body weight increased gradually and then stabilized at 11 to 12 kg above the weight at the end of the hospital stay.

End-systolic wall stress (Fig. 3). End-systolic wall stress was in the normal range at the end of hospitalization. Over the ensuing months it gradually increased by 30% to 40% and then stabilized.

LV wall thickness (Table II). Both septal and p sterior wall thickness decreased in the initial months after transplant: after 6 months septal thickness decreased by 0.8 ± 0.4 mm ($p < 0.05$) and posterior wall thickness by 0.7 ± 0.3 mm ($p < 0.05$), and then stayed at this level.

LV mass (Fig. 4). At the end of the hospital stay, LV mass (in absolute values or corrected for body surface area) was in the high-normal range. Within the next few months the left ventricle decreased in weight by 30 to 40 gm ($p < 0.05$) or 25 to 30 gm/m^2 ($p < 0.01$) and over the remaining 9 months remained at a lower normal level.

Biochemical parameters

Plasma catecholamines. Both plasma norepinephrine and epinephrine levels were in the normal range a few weeks after surgery and remained so during the year of follow-up (Table III).

PRA. PRA was in the high-normal range shortly after surgery and showed small increases over the year of follow-up, mainly related to one patient with high PRA (Table III).

Serum and urinary electrolytes and renal function (Table IV). Electrolytes were in the normal range throughout the study (only the urinary sodium concentration is shown). Serum creatinine and creatinine clearance were already slightly abnormal early after surgery and showed further deterioration between 1 and 3 and 6 and 9 months of follow-up.

DISCUSSION

Development of hypertension after heart transplant in patients taking cyclosporine for immuno-

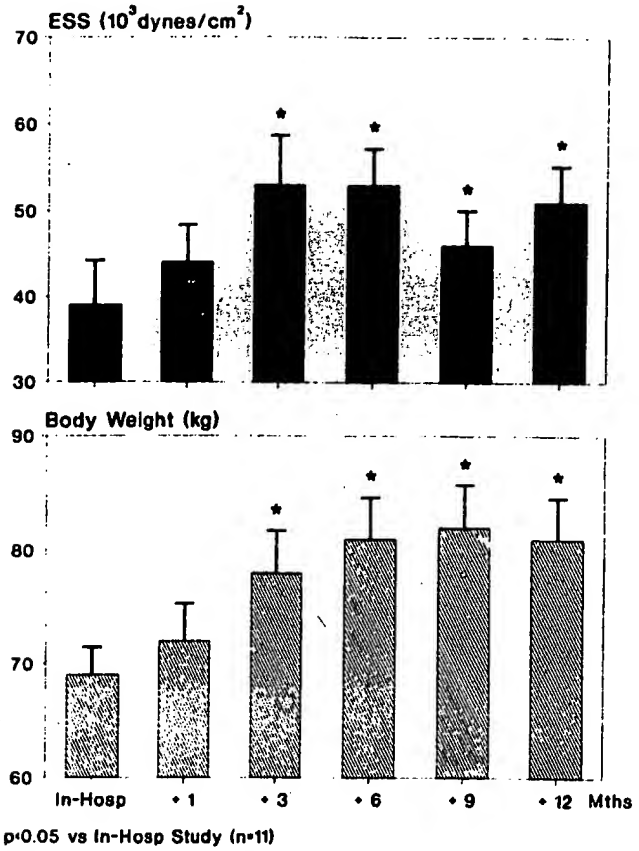

Fig. 3. LV end-systolic wall stress *(ESS)* and body weight after heart transplant. Values represent means ± SEM (n = 11). $*p < 0.05$ for change from in-hospital study.

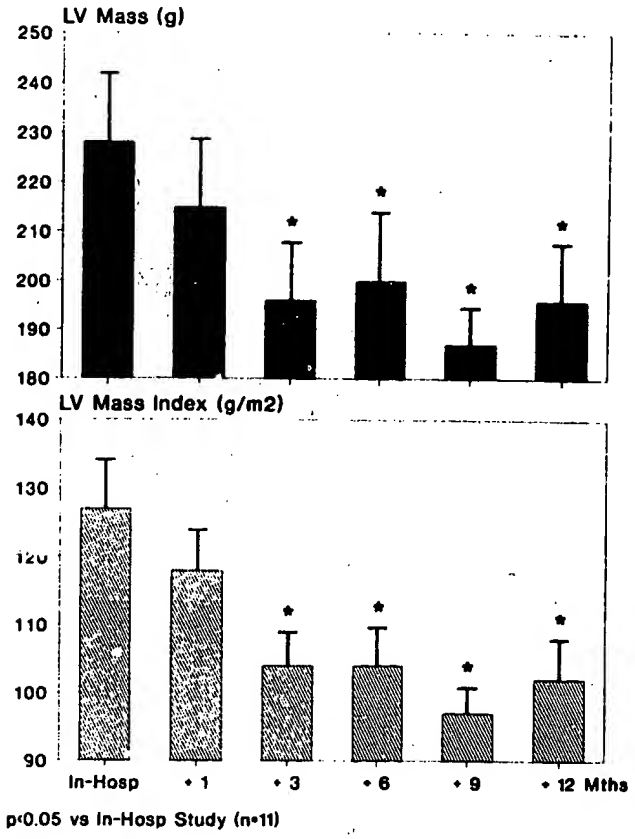

Fig. 4. LV mass and LV mass index after heart transplant. Values represent means ± SEM (n = 11). $*p < 0.05$ for change from in-hospital study.

suppression is a well-established phenomenon.[14] Blood pressure starts to increase within weeks after transplant[6, 15] and may increase to moderate and occasionally severe levels. In the present study hypertension developed in almost all patients, and despite treatment with one or two antihypertensive drugs (Table I) blood pressure remained in the mildly hypertensive range. Moreover, the actual chronic blood pressure load is higher as compared with that in patients with mild to moderate essential hypertension, since nighttime blood pressure remains at the level of daytime blood pressure in patients with heart transplants.[16] With regard to the general hemodynamic changes causing the increase in blood pressure, one study[15] reported an increase in cardiac output early after heart transplant; otherwise, as in the present study, increases in TPR with no or small decreases in stroke volume and cardiac output have been observed consistently.[6, 17] The decrease in stroke volume appears to relate to both a decrease in LV end-diastolic volume and the increase in afterload decreasing fractional shortening and increasing LV end-systolic volume, a pattern of changes previously described by, for example, Murali et al.[17] The decrease in end-diastolic volume rather than the increase expected from the decreased LV emptying may relate to the development of myocardial fibrosis affecting the end-diastolic pressure-volume relationship.[17]

The actual mechanisms involved in the increase in TPR after heart transplant are still controversial.[18] Sympathetic activity as assessed by plasma catecholamine levels does not increase[6, 19-21] (and present study). However, this does not exclude selective increases in sympathetic nerve activity to specific tissues, organs, or both.[22] No increases in the activity of the renin-angiotensin system have been reported[14, 23] (and present study). It is possible that the increases in renal and systemic vasoconstriction are related to a potentiating effect of cyclosporine on pressor responses to vasoconstrictor hormones.[24] This effect may be a result of an exaggerated increase in the intracellular calcium level in response to stimulation.[25] In addition, cyclosporine may alter the balance of

Table III. Plasma catecholamine levels and PRA during the first year after heart transplant

	In hospital	*+1 mo*	*+3 mo*	*+6 mo*	*+9 mo*	*+12 mo*
Plasma norepinephrine (pg/ml)						
Supine	276 ± 35	317 ± 48	296 ± 35	317 ± 62	312 ± 49	293 ± 30
Standing						
5 min	564 ± 83	591 ± 102	643 ± 57	669 ± 93	594 ± 92	627 ± 101
15 min	615 ± 73	687 ± 118	714 ± 69	799 ± 151	713 ± 94	698 ± 89
Plasma epinephrine (pg/ml)						
Supine	45 ± 6	42 ± 7	51 ± 7	54 ± 6	59 ± 6	53 ± 6
Standing						
5 min	62 ± 9	49 ± 4	74 ± 19	61 ± 6	75 ± 12	65 ± 8
15 min	61 ± 8	50 ± 8	71 ± 13	64 ± 8	71 ± 9	60 ± 8
PRA (ng/ml/hr)						
Supine	5.9 ± 1.8	4.6 ± 2.6	6.4 ± 2.4	8.0 ± 2.7	8.0 ± 2.8	5.1 ± 1.4
Standing						
5 min	7.4 ± 2.1	5.2 ± 2.7	7.4 ± 3.3	8.5 ± 2.9	10.0 ± 3.8	6.2 ± 1.8
15 min	8.0 ± 2.5	6.5 ± 3.4	8.3 ± 3.9	9.5 ± 2.8	10.8 ± 3.7	6.5 ± 1.9

Values represent means ± SEM (n = 10 to 13).

Table IV. Renal function and urinary sodium excretion during the first year after heart transplant

In hospital	*+1 mo*	*+3 mo*	*+6 mo*	*+9 mo*	*+12 mo*
Serum creatinine (umol/L)					
115 ± 12	116 ± 13	140 ± 17	143 ± 10*	168 ± 14*	170 ± 11*
Creatinine clearance (ml/min/1.73m^2)					
77 ± 9	76 ± 9	66 ± 5	66 ± 6	59 ± 7*	54 ± 6*
24-Hour urinary sodium excretion (mmol/day)					
158 ± 23	170 ± 13	187 ± 17	188 ± 17	166 ± 22	146 ± 16

Values represent means ± SEM (n = 10 to 13).
*$p < 0.05$ for change from in-hospital study.

prostacyclin–thromboxane A_2 generation resulting in vasoconstriction.[18]

The major new finding emerging from the present study is that hypertension after heart transplant is not associated with development of LV hypertrophy. In an evaluation of the time-course of the changes in LV mass after heart transplant, two phases emerge. During the initial weeks after transplant significant decreases in LV mass occur. Considering that preload and afterload were likely higher in the older recipients than the younger donors, donor-recipient hemodynamic mismatch would tend to increase rather than decrease LV mass. It is more likely that the loss of mass represents disappearance of interstitial edema. LV wall thickness and myocardial volume (but not end-diastolic volume) are markedly increased 1 week after transplant, as compared with values obtained just bef re don r cardiectomy, the extent of the increase correlating with the ischemic time.[26] The most likely explanation proposed is myocardial edema caused by pr l nged cold ischemia. This edema appears to disappear gradually over the ensuing weeks,[26] resulting after 2 to 3 months in a normal LV mass[7] (and present study). Rejection does not appear to play a major role, since on biopsy little evidence of rejection was present (see Methods) and only more marked rejection increases LV mass.[7, 27] In the second phase, after the disappearance of this, presumably, myocardial edema LV mass was found to be in the truly normal range (about 100 gm/m^2) and remained so for at least 1 year with not even a tendency toward an increase. Considering our reproducibility data with a 3% variation for repeated measurements,[4] only a minor increase may have been missed. Two cross-sectional studies reported small increases in LV mass: +14% (NS) in 13 patients >12 weeks after transplant compared with 30 control subjects,[7] and +17% ($p < 0.05$) in 10 patients 1.2 ± 0.8 years after transplant compared with 10 control subjects.[8] Both studies actually report similar values for LV mass as noted in the present study. The appropriate control is thus crucial in determining whether these values are in the normal range or increased. Borow et al.[8] studied "10 healthy subjects matched for donor heart age." However, sex and body mass are also important determinants of LV mass[28]

and were not controlled in their study. McKoy et al.[7] reported a nonsignificant difference in a retrospective study f patients who happened to undergo echocardiographic studies; they did control for sex but not for body mass.

In a general population with hypertension the combination of increases in systolic blood pressure and body mass as observed in the present study substantially increases the prevalence of LV hypertrophy.[28, 29] The question then is why no increase at all was noted in the patients with heart transplants. There are several possible explanations. First, most patients used antihypertensive drugs particularly in the latter part of the study. Even in denervated hearts some of these drugs may have influenced the relationship between hemodynamic load and myocardial growth. Second, sympathetic blockade can prevent and/or ameliorate some forms of cardiac hypertrophy, such as that induced by minoxidil or exercise,[30, 31] but not other forms.[5] There is extensive evidence that after heart transplant the left ventricle remains denervated for a prolonged period of time.[32, 33] It is thus tempting to propose that in the absence of cardiac sympathetic nerve activity larger increases in hemodynamic load are required to increase myocardial mass. Finally Kahan[18] postulated that cyclosporine inhibits gene transcription of critical humoral regulators. Such an effect may extend to induction of proto-oncogenes in response to pressure overload. The other immunosuppressive agents (azathioprine and prednisone) may also possibly inhibit one r more of the steps leading to hypertrophy. In conclusion, the present study shows that the development of hypertension after heart transplant is *not* associated with development of LV hypertrophy, indicating that either the increase in hemodynamic load was not sufficient or its trophic effect was prevented.

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Immediate blood pressure effects of the renin inhibitor enalkiren and the angiotensin-converting enzyme inhibitor enalaprilat

The antihypertensive effects of the renin inhibitor enalkiren were compared with those of the angiotensin-converting enzyme inhibitor enalaprilat in 17 hypertensive patients (14 white, 3 black; mean age 57 years) whose renin systems had been stimulated by diuretic pretreatment. Patients were studied on 3 separate in-hospital days. On the first study day patients received placebo alone. On day 2 they received intravenous bolus doses of enalkiren (0.03 to 1.0 mg/kg), and on day 3, intravenous bolus doses of enalaprilat (0.625 to 1.25 mg). Each agent reduced systolic ($p < 0.01$) and diastolic ($p < 0.01$) blood pressures (BP) from baseline levels. The acute decrease in systolic BP of 18.5 ± 0.4 mm Hg during enalkiren tended to be greater ($p < 0.01$) than the decrease of 12.6 ± 0.7 mm Hg during enalaprilat. Decreases in diastolic BP during enalkiren (11.9 ± 0.4 mm Hg) were also slightly greater ($p < 0.1$) than those during enalaprilat (9.2 ± 0.4 mm Hg). Based on prestudy plasma renin activity (PRA), patients were divided into "high" renin (PRA >3.5 ng angiotensin I/ml/hr; $n = 6$) and "low/normal" renin (<3.5 ng angiotensin I/ml/hr; $n = 11$) groups. Reductions in diastolic BP in the "high" renin group during enalkiren (30 ± 5/20 ± 3 mm Hg) tended to be greater ($p < 0.07$) than those during enalaprilat (23 ± 7/14 ± 1 mm Hg); differences were not significant in the "low/normal" group (12 ± 2/7 ± 2 and 7 ± 2/8 ± 1 mm Hg, respectively). Thus the renin inhibitor is at least as effective as the ACE inhibitor in its immediate BP-lowering effects in hypertensive patients. (Am Heart J 1991;122:1094.)

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The renin-angiotensin system has been established as a regulator of cardiovascular homeostasis, and the clinical efficacy of angiotensin-converting enzyme inhibitors has underscored the role of this system in sustaining arterial hypertension. The development of highly specific, direct inhibitors of renin, the enzyme catalyzing rate-limiting step in the renin-angiotensin